

Evaluation of Gender and Smoking Status Differences on the Pharmacokinetics (PK) of Nicotine (NICO) and Cotinine (COT) after Intranasal Nicotine Administration

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Abstract

- **PURPOSE:** To study the PK profile of NICO and COT in plasma following a single dose of nicotine nasal spray with respect to smoking status and gender.
- **METHODS:** A clinical study in 18 healthy volunteers (age: 21-35) was conducted in 6 nonsmokers (NS), 6 light-smokers (LS), 6 heavy-smokers (HS), categorized by their reported smoking history and nicotine dependence (3 males (M) and 3 females (F) per group). One mg of NICO (Nicotrol®) was administered intranasally. Smokers had to refrain from smoking 15 hours prior to and 6 hours after drug administration. Venous blood samples were taken at -30, 0, 2.5, 5, 7.5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 180, 240, 360 minutes relative to dosing time. Plasma samples were frozen at -20°C until assayed. Triple liquid-liquid extraction was performed to extract NICO and COT from plasma and consequently analyzed via a validated GC-MS method. The limit of quantitation was 1.0 ng/ml for both NICO and COT. Noncompartmental PK analysis was performed. Two-way ANCOVA was done on the log-transformed exposure metrics including baseline (BL) NICO or COT as covariate.
- **RESULTS:** No differences were found for any of the NICO PK parameters by gender or smoking status. Apparent PK differences for COT between the two smoking groups compared to the NS group were attributable to differences in baseline COT; no gender difference was found.
- **CONCLUSIONS:** There are no differences in PK of NICO or COT after intranasal administration across smoking status or gender. Parts of the study were supported by the A.D. Williams Trust Fund, VCU and the General Clinical Research Center Grant M01 RR00065, NCRR, NIH.

Introduction

NICO dependence is a major health concern in the United States as well as all around the world. In 1999, approximately 46.5 million adults in the United States reported smoking¹. With a slight decline in adult smokers in the past few years, there have been rises in numbers of teenagers and women taking up smoking¹.

Over the years, there have been differences in smoking habits found. Some differences exist between males and females in terms of rate of smoking as well as rate of quitting². A recent study suggests that females receive more of an anxiolytic effect from nicotine than males³. Furthermore, other studies demonstrated that males had higher quit rates than females^{4,5}.

Differences have also been found between smokers as some individuals smoke more and are more dependent on NICO than others⁶. Some smokers tend to smoke in moderate amounts, and some even less frequently than heavy-smokers that smoke at least a pack of cigarettes a day.

This study seeks to investigate whether gender or smoking status differences exist in the pharmacokinetics of NICO or COT that may explain some of these behavioral differences.

Purpose

- To provide detailed plasma concentration time profiles after nicotine nasal spray for:
 - nicotine (NICO)
 - cotinine (COT)
- To characterize systemic exposure to NICO and COT (AUC_{0-6hr} , C_{max} , t_{max})
- To determine if smoking history or gender has an effect on NICO/COT exposures

Study Design

- Double-blind, randomized, placebo-controlled, two-treatment crossover

Sequence	Period 1	Period 2
A	Placebo	1 mg NNS
B	1 mg NNS	Placebo

- n = 18 healthy young volunteers (21-35 yo)
9 males and 9 females

Smoking Status Classification

Subject Group	Inclusion/Exclusion Criteria
Nonsmokers (NS) 3M:3F	1. No current tobacco use 2. Not a smoker for the past 5 years 3. If previously a smoker, did not smoke more than one occasion over a 1 year continuous time period 4. FTND* score = 0
Light-smokers (LS) 3M:3F	1. Current smoker of cigarettes (No other tobacco products) 2. Smokes between 5-15 cigarettes/day 3. Has been smoking for at least an entire 1 year time period 4. FTND score = 1 - 6
Heavy-smokers (HS) 3M:3F	1. Current smoker of cigarettes (No other tobacco products) 2. Smokes between 20 cigarettes/day 3. Has been smoking for at least an entire 1 year time period 4. FTND score = 1 - 10

*FTND = Fagerström Test for Nicotine Dependence⁷

Study Design

- Telephone screening
 - smoking history, FTND score, medical history.
- History and Physical Exam
 - blood and urine tests, EKG, DAU, β -HCG.
- Treatment Period 1
 - Admission to GCRC the evening before dosing.
Smoking restriction 15 hours prior to dosing.
- Treatment Period 2 and Exit Physical Exam
 - same as period 1, different medication

Sampling Schedule

- Blood was collected at the following time points:
-30, 0, 2.5, 5, 7.5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 180, 240 and 360 minutes relative to dosing time.
- Blood was centrifuged for 10 minutes at 3000 rpm.
- Plasma was removed and two 2mL tubes were aliquoted.
- Plasma samples were stored at -20 °C until assayed.

Sample Analysis

- Nicotine and cotinine plasma assay:
 - triple liquid/liquid extraction
 - Gas Chromatography/Mass Spectrometry
 - LOQ:
 - nicotine: 1 ng/mL
 - cotinine: 1 ng/mL
 - Figures of Merit

		Nicotine (ng/mL)			Cotinine (ng/mL)		
		2	8	40	2	50	400
Accuracy	Interrun	0.8%	0.5%	13.7%	1.8%	4.2%	8.4%
	(%DFN) Intrarun	17.2%	3.3%	10.4%	19.8%	13.9%	3.1%
Precision	Interrun	11.3%	5.0%	5.6%	11.8%	7.3%	5.4%
	(%COV) Intrarun	4.3%	2.7%	5.1%	12.7%	5.1%	4.6%

PK Metrics

- PK metrics
 - C_{\max} (ng/mL)
 - T_{\max} (hr)
 - AUC_{0-6hr} (ng/mL)hr
 - BL (ng/mL): The mean of the two baseline measurements

- Statistical Analysis

Two-way ANCOVA for log-transformed metrics

Factors: smoking history and gender

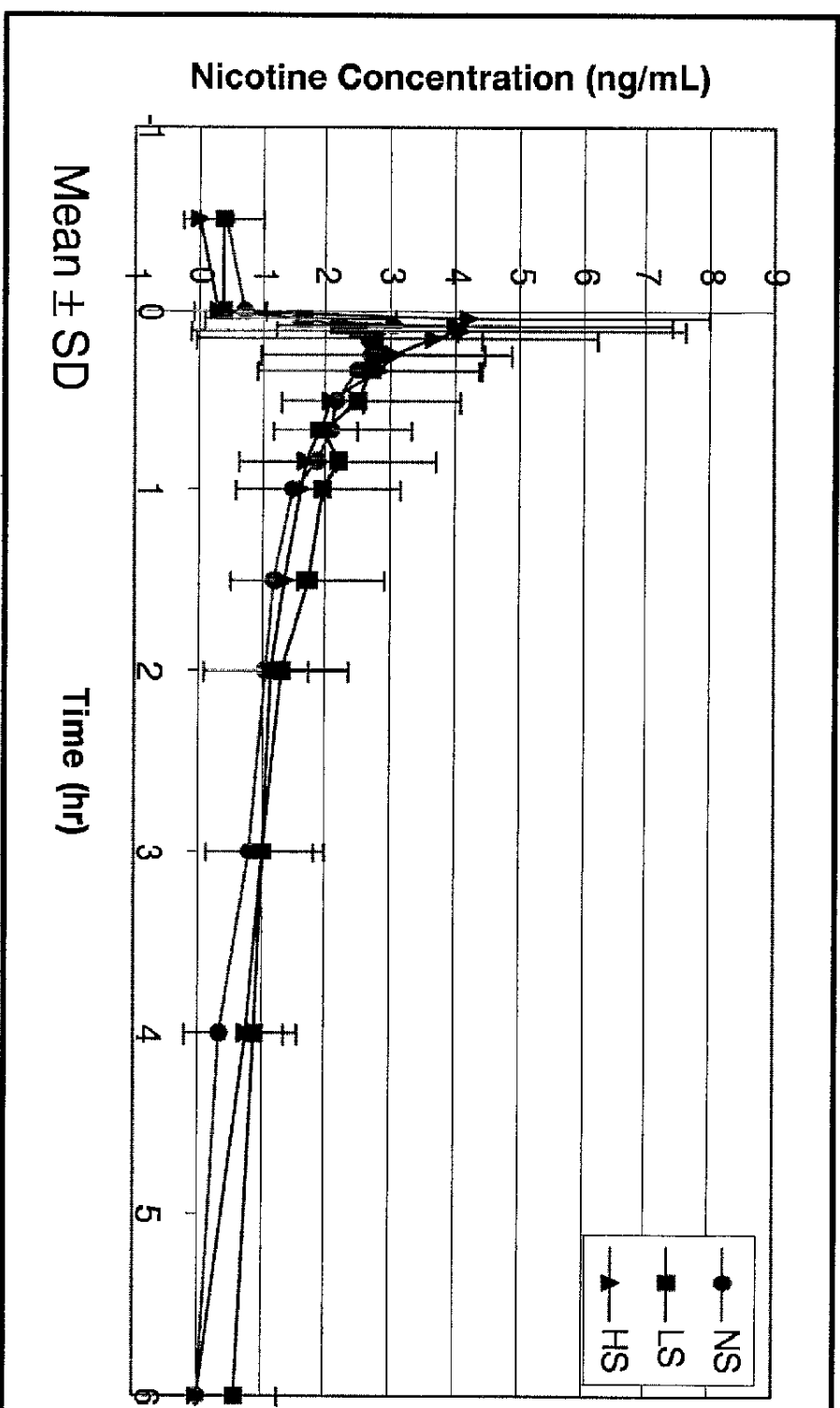
Covariate: baseline (only for cotinine)

Nicotine PK Summary

Smoking Status		C_{\max} (ng/mL)	T_{\max} (hr)	$AUC_{0-6\text{hrs}}$ (ng/mLhr)
NS	M	3.4 (56%)	0.3 (100%)	3.9 (80%)
	F	4.5 (53%)	0.1 (0%)	6.8 (31%)
LS	M	3.6 (36%)	0.2 (50%)	7.1 (63%)
	F	2.8 (86%)	2.2 (150%)	12.2 (18%)
HS	M	2.7 (22%)	0.1 (0%)	5.3 (49%)
	F	6.4 (72%)	0.1 (100%)	7.7 (28%)

Mean \pm %COV

Results: Nicotine



Cotinine PK Summary

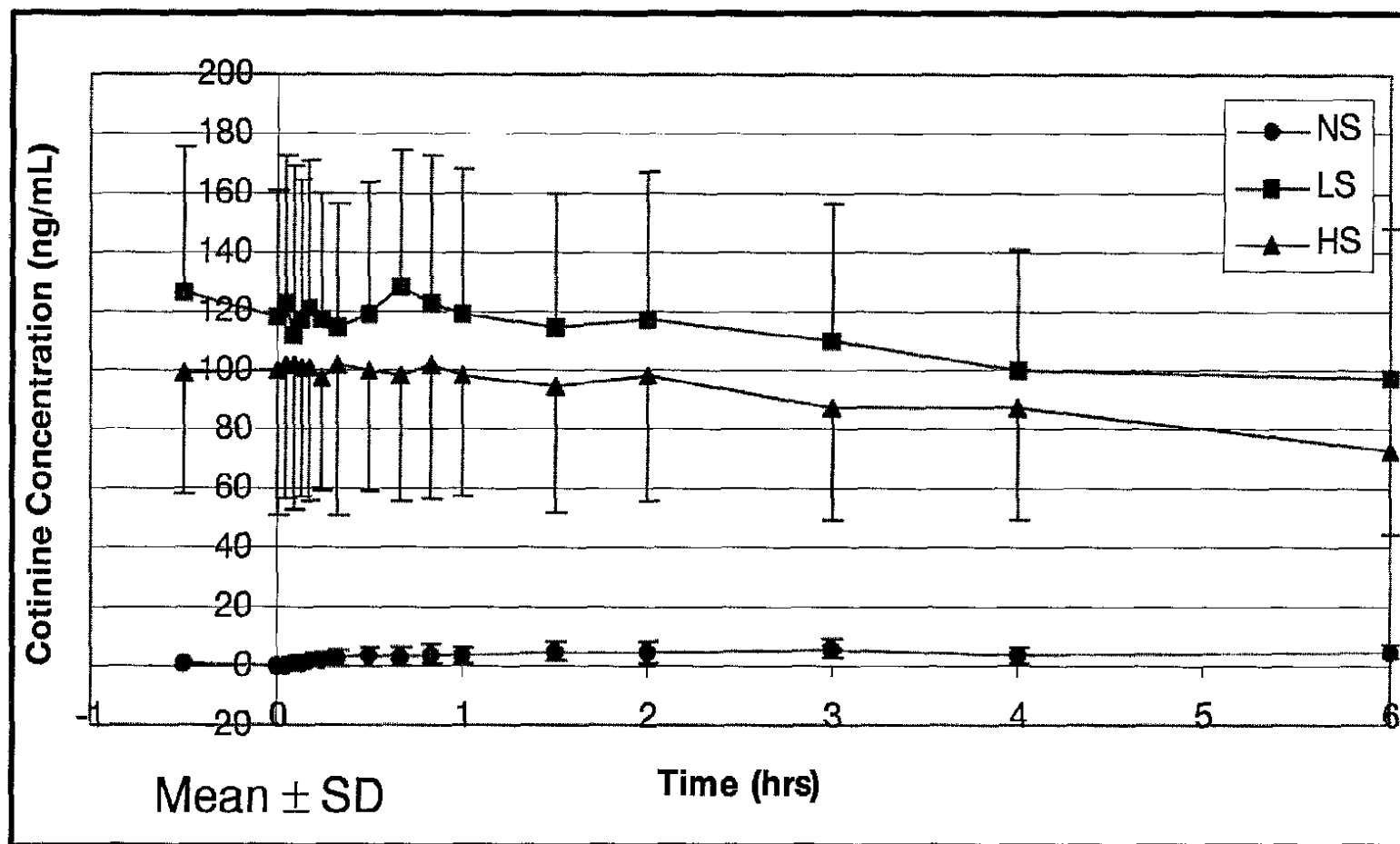
Smoking Status		BL (ng/mL)	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-6hrs} (ng/mLhr)
NS	M	0.4 (75%)	4.3 (35%)	4 (50%)	19 (42%)
	F	0.4 (100%)	8.0 (45%)	3 (20%)	31 (39%)
LS	M	134 (46%)*	141 (45%)	0.6 (50%)	736 (48%)
	F	110 (32%)*	112 (33%)	0.4 (125%)	579 (37%)
HS	M	115 (56%)*	124 (57%)	0.2 (50%)	619 (54%)
	F	85 (16%)*	93 (17%)	1.0 (90%)	462.6 (16%)

*

*

Mean ± %COV * p< 0.001 NS < (LS = HS) before BL covariate

Results: Cotinine



Mean ± SD

Time (hrs)

PK Summary

- There were no differences in NICO exposure between smoking groups or by gender.
- Measurable COT were levels present prior to dosing (BL).
 - Smokers (HS, LS) > NS
- Apparent differences between smoking groups in COT exposure were fully attributed to baseline levels. No gender differences were found

Overall Conclusions

- Smoking history is reflected in BL COT levels (consistent with reported half-life of 14-16 hrs⁸).
 - Smokers > Nonsmokers
 - No difference between LS and HS
- The study results suggest that neither smoking history nor gender affect the intrinsic NICO or COT PK after intranasal NICO administration.

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